

H pylori related diseases :
peptic ulcer, MALT lymphoma, gastric cancer.
Long term effect of *H pylori* eradication

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Reinfection rate after successful eradication

- Recurrence one year after eradication (recrudescence)
 - developed countries: 2.67%
 - developing countries: 13.00%
- Annual recurrence after longer follow-up in patients with negative UBT a year after eradication
 - developed countries: 1.45%
 - developing countries: 12.00%

Peptic ulcer

Ulcer recurrence after eradication therapy

- Spontaneous yearly relapse rate:
 - Duodenal ulcer: 80%
 - Gastric ulcer: 60%
- yearly relapse rate after *H pylori* eradication:
 - Duodenal ulcer: 5%
 - Gastric ulcer: 5%

Eradication therapy in *H pylori* positive peptic ulcer disease: systematic review

Ford AC *Am J Gastroenterol* 2004; 99: 1833

Variable	Value	Uncertainty
Healing rate of DU with H ₂ RA	85%*	95% CI = 81 to 88%*
Healing rate of GU with H ₂ RA	89%*	95% CI = 84 to 93%*
Annual relapse rate of DU on no treatment	64%*	95% CI = 57 to 70%*
Annual relapse rate of GU on no treatment	57%*	95% CI = 34 to 57%*
RR of DU relapse after <i>H. pylori</i> eradication	0.20*	95% CI = 0.15 to 0.26*
RR of GU relapse after <i>H. pylori</i> eradication	0.28*	95% CI = 0.18 to 0.43*
RR of DU and GU relapse with maintenance	1.37*	95% CI = 0.8 to 2.37*
H₂RA versus <i>H. pylori</i> eradication		
RR of adverse event with <i>H. pylori</i> eradication	2.28*	95% CI = 1.72 to 3.02*
Cost per patient of managing ⁽⁶⁹⁾ adverse event	\$115	SD =\$115**
Proportion symptomatic despite peptic ulcer healing	33%†	95% CI = 25% to 43%

Gastric MALT lymphoma

Endoscopy



**Superficial
lesions
30%**

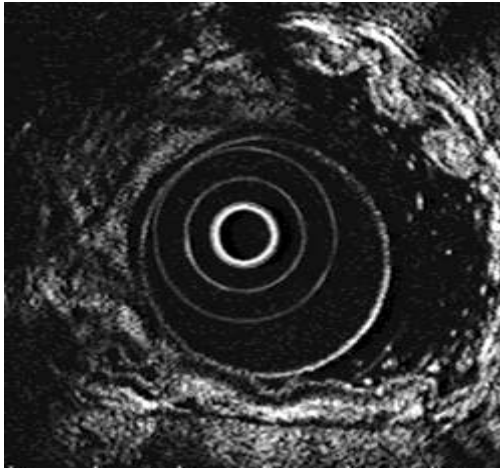


**Ulcers
45%**

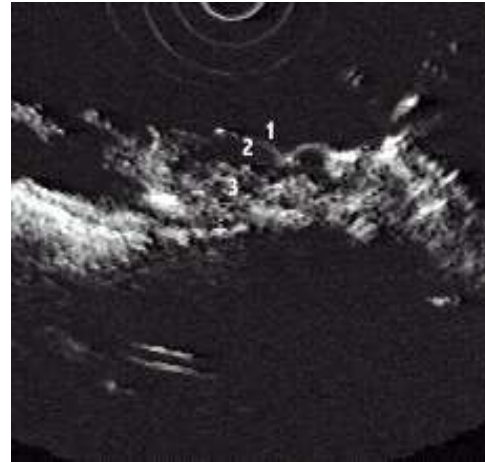


**Thickened
folds
25%**

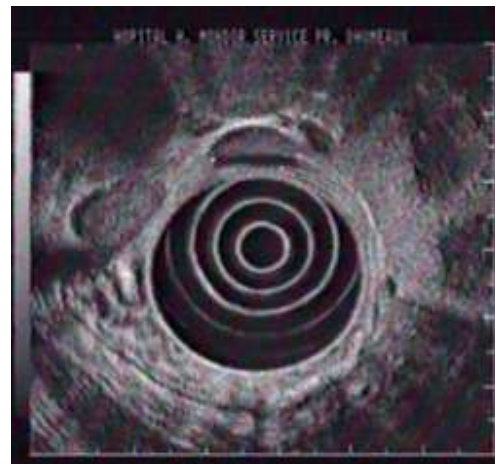
Endoscopic ultrasonography



Normal
45 to 70%



5 mm (6 à 12)
10 to 50%



Lymph nodes
10 to 30%

Response to *H pylori* eradication according to staging

Authors	Year	n	Initial* stage	Staging procedures	Complete remission Rate % (n)	Median Follow-up (m range)	Relapses (n)
Savio	1996	12	IE	CT	84 (11)	24 (14-36)	0
Neubauer	1997	50	IE	CT+ EUS	80 (40)	15 (0-40)	5
Pinotti	1997	45	IE	CT	68 (30)	23 (2-66)	2
Montalban	1997	9	IE	CT	88 (8)	14 (7-22)	?
Nobre Leitao	1998	17	IE	CT + EUS	100 (17)	12 (2-39)	1
Steinbach	1999	28	IE+IIE	CT or EUS	50 (14)	(> 18)	0
		23	IE		56 (13)		
Ruskoné	2001	34	IE+IIE ₁	CT + EUS	56 (19)	23 (8-44)	2
		24	IE		79 (19)		
Lévy	2002	48	IE+IIE ₁	CT+ EUS	58 (28)	34 (6-60)	0
		33	IE		76 (25)		

*Ann Arbor staging system, EUS :endoscopic ultrasonography ; CT : abdominal computed tomography

Correlation between t (11;18) and response to *H. pylori* eradication

	n	Response to <i>H. pylori</i> eradication	t(11;18)	(%)
Liu et al Gastroenterology 2002	111	48 R 63 NR	2* 42	4 67

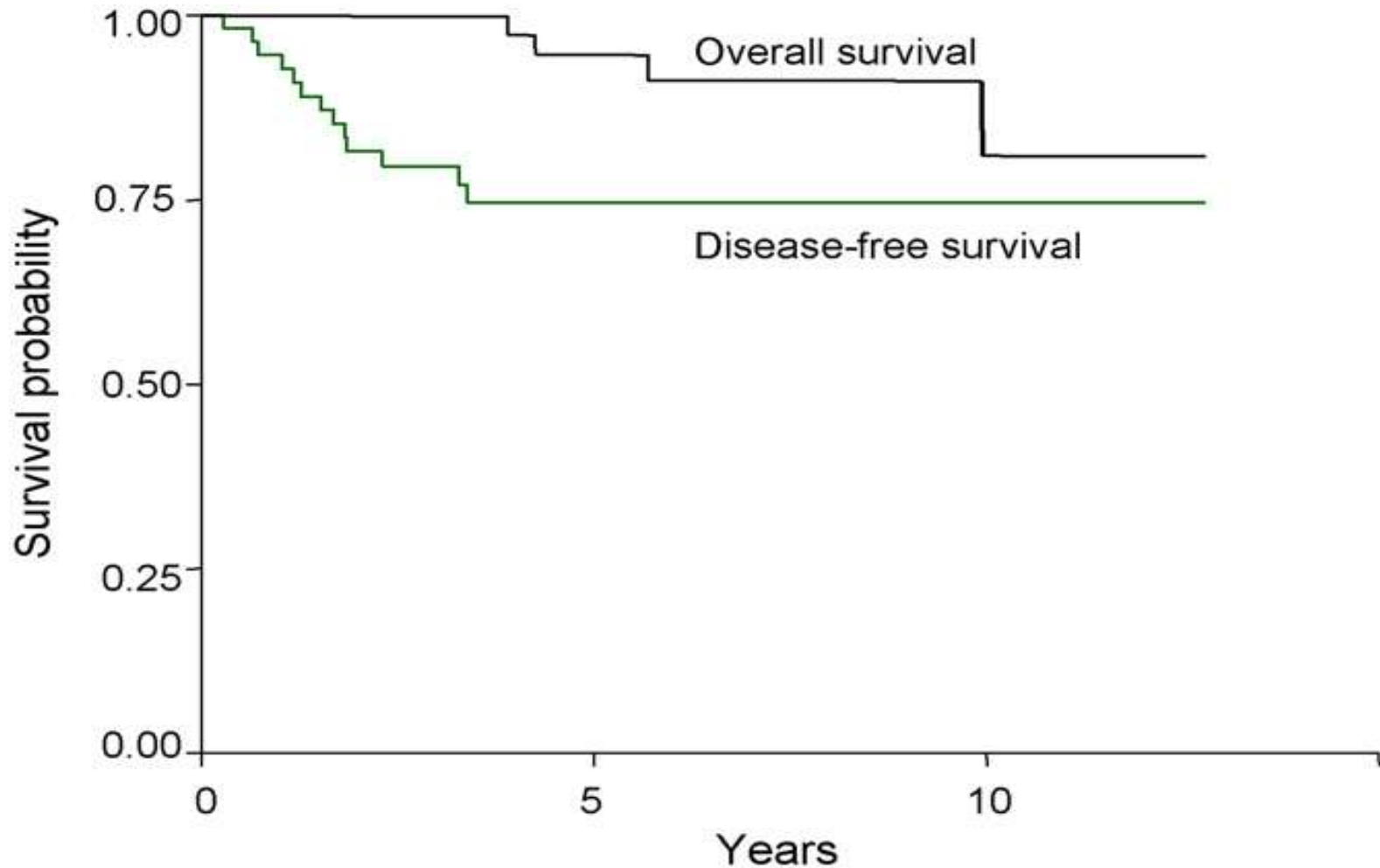
R : Responder

NR : Non responder

* These patients had lymphoma relapse.

Overall survival and disease-free survival of patients with early stage *H pylori* positive gastric MALT lymphomas

Andriani A *Dig Liver Dis* 2009; 41: 467



LONG-TERM FOLLOW-UP OF REpondERS TO *H PYLORI* ERADICATION

- Long-term stability of the endoscopical response
- Persisting clonality: 40 %.
- Fluctuations of histological and/or molecular results.
Isaacson et al, gastroenterology 1999, Pinotti G et al, Ann Intern Med 2000, Thiede C et al, Rec Res Cancer Res 2000, Savio A et al, Rec Res Cancer Res 2000, Montalban C et al, Ann Oncol 2005
- Persisting histological residual disease for several years in some patients
Fischbach W et al Gut 2007
Watch-and-wait strategy in these cases
- Transformation to a high grade lymphoma: very rare

Increased risk for metachronous gastric cancer

After *H pylori* eradication \pm radiotherapy or chemotherapy

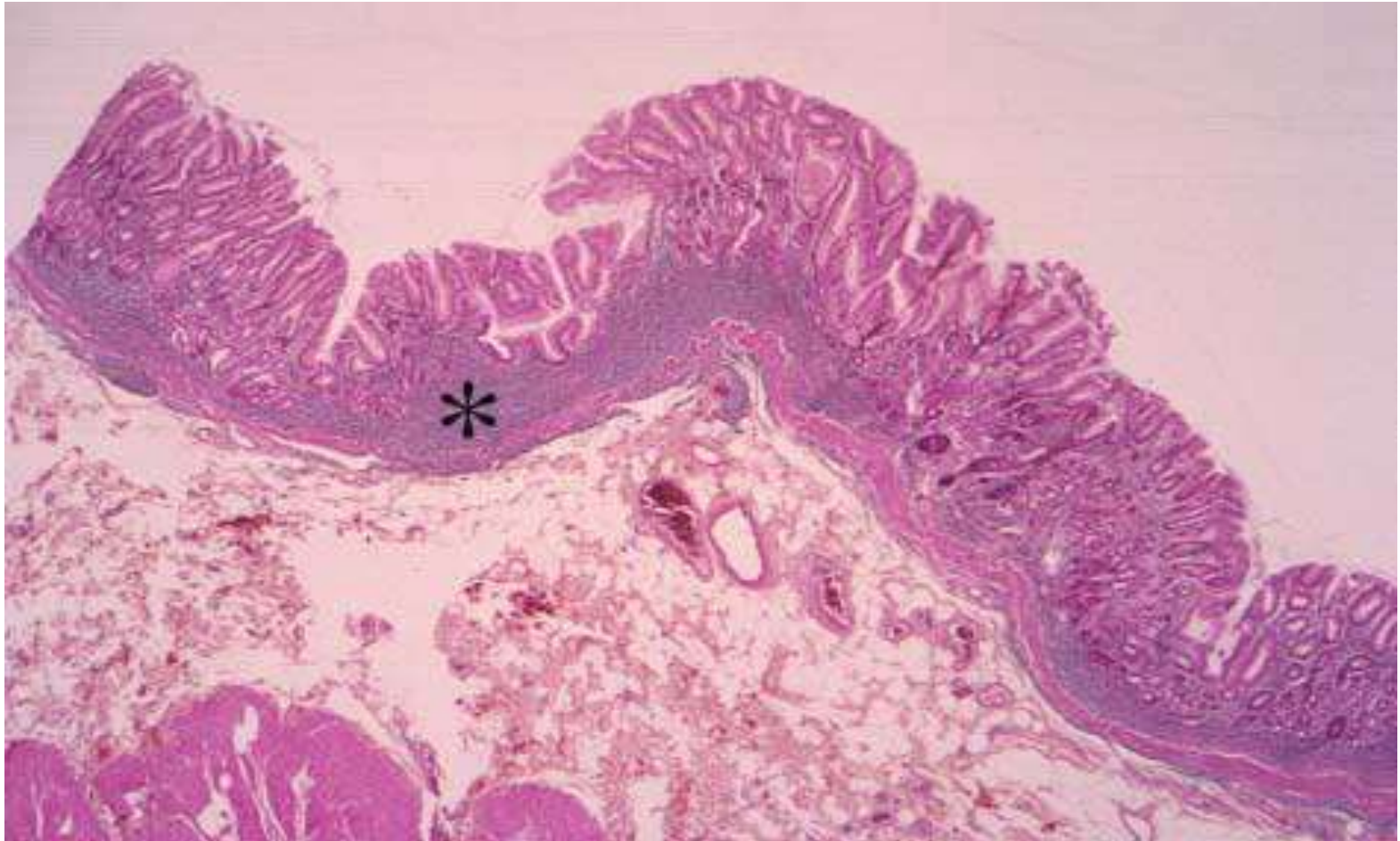
Morgner A World J Gastroenterol 2001;7(2):248-53.

Ono S J Gastroenterol Hepatol 2010;25:804

Copie-Bergman C Ann Oncol 2005;16(8):1232-6.

Occurrence of premalignant disease (atrophy, intestinal metaplasia)

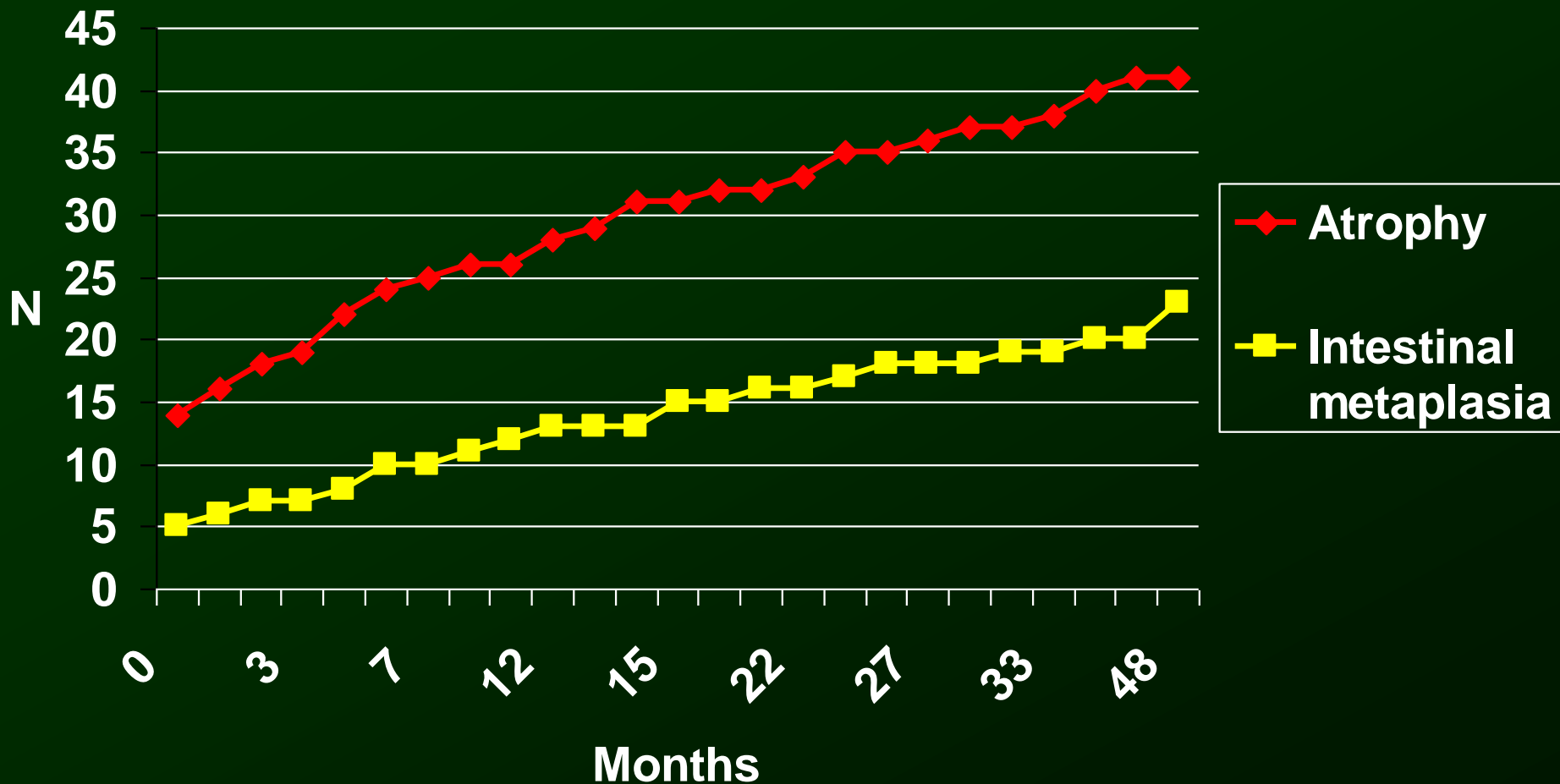
Copie-Bergman C Ann Oncol 2005;16(8):1232-6



residual MALT lymphoma (asterisk) in the corpus, in the deep part of the mucosa. Haematoxylin and eosin stained section.

Conservative treatment of gastric MALT lymphoma: rapid progression of atrophy and intestinal metaplasia

Cohort from H Mondor hospital: Lamarque et al Am J Gastroenterol 2006, 101:1886



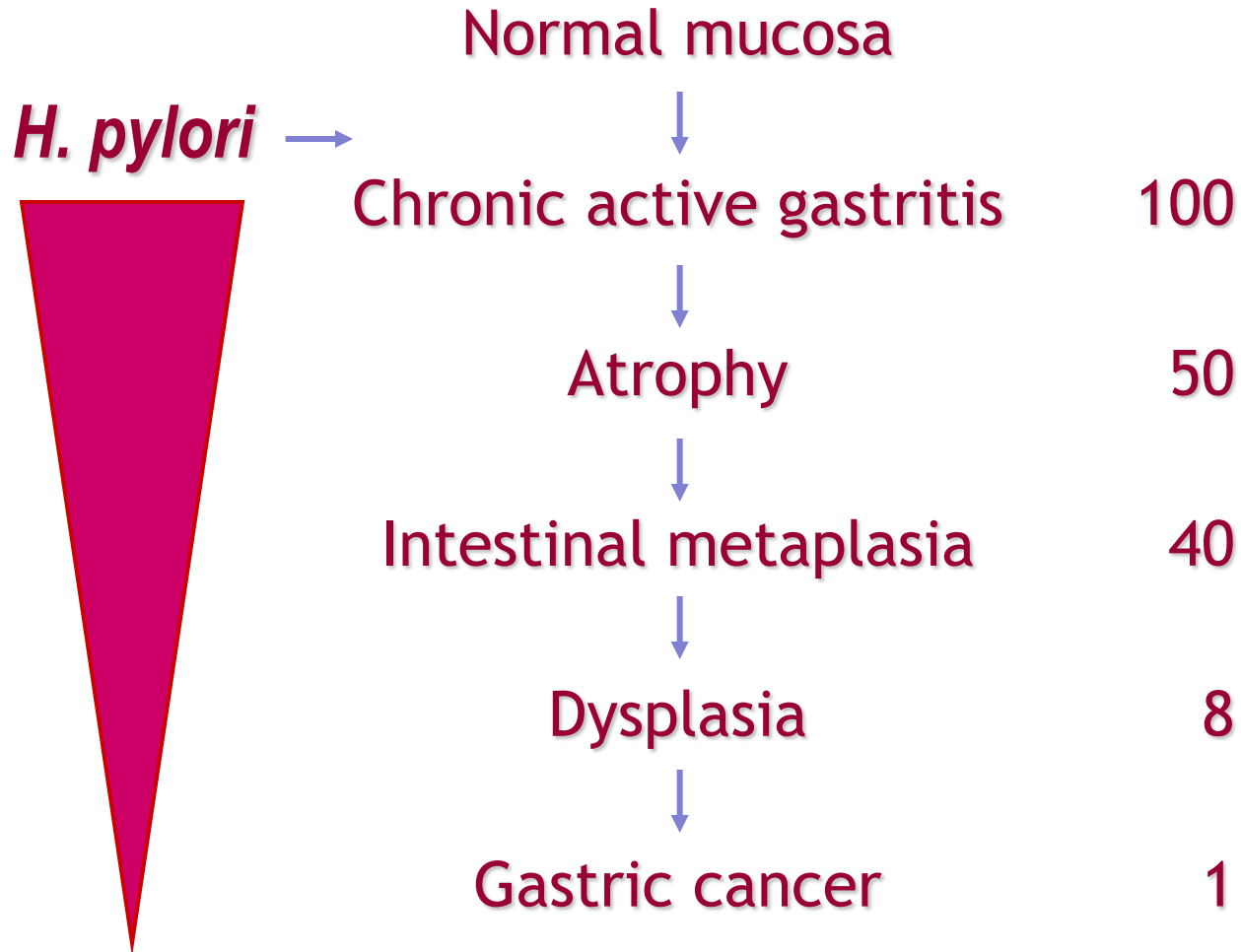
Gastric MALT lymphoma

Take home messages

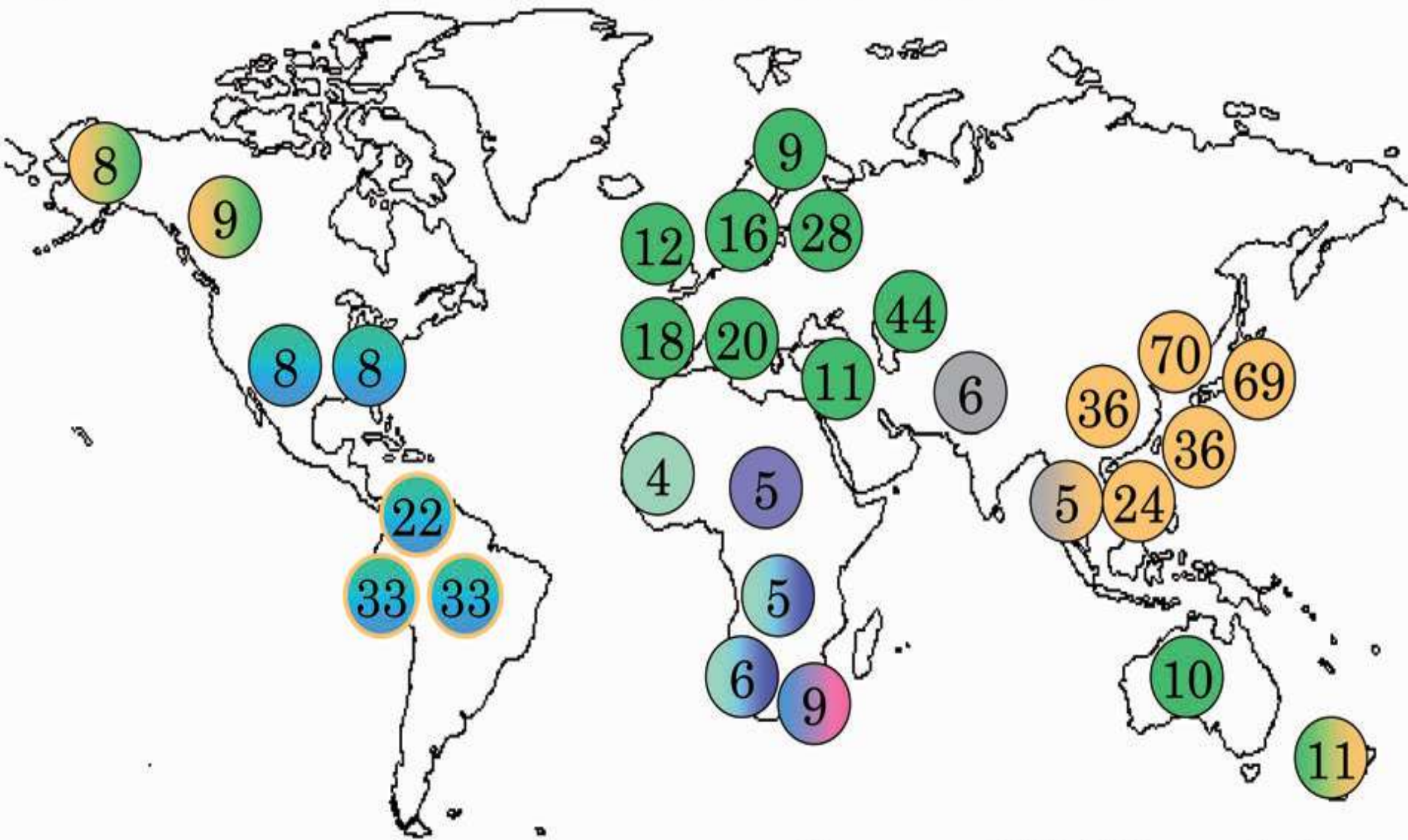
- Most of gastric MALT lymphomas respond to *H pylori* eradication
- Factors of non response:
 - extension to lymph nodes at EUS
 - translocation t(11;18)
- Stability of the response
- Main risk at long-term follow-up: gastric adenocarcinoma
- Close follow-up with endoscopy + histology should be performed every 6 months for two years, then every year.

Gastric Cancer

Histological steps in carcinogenesis

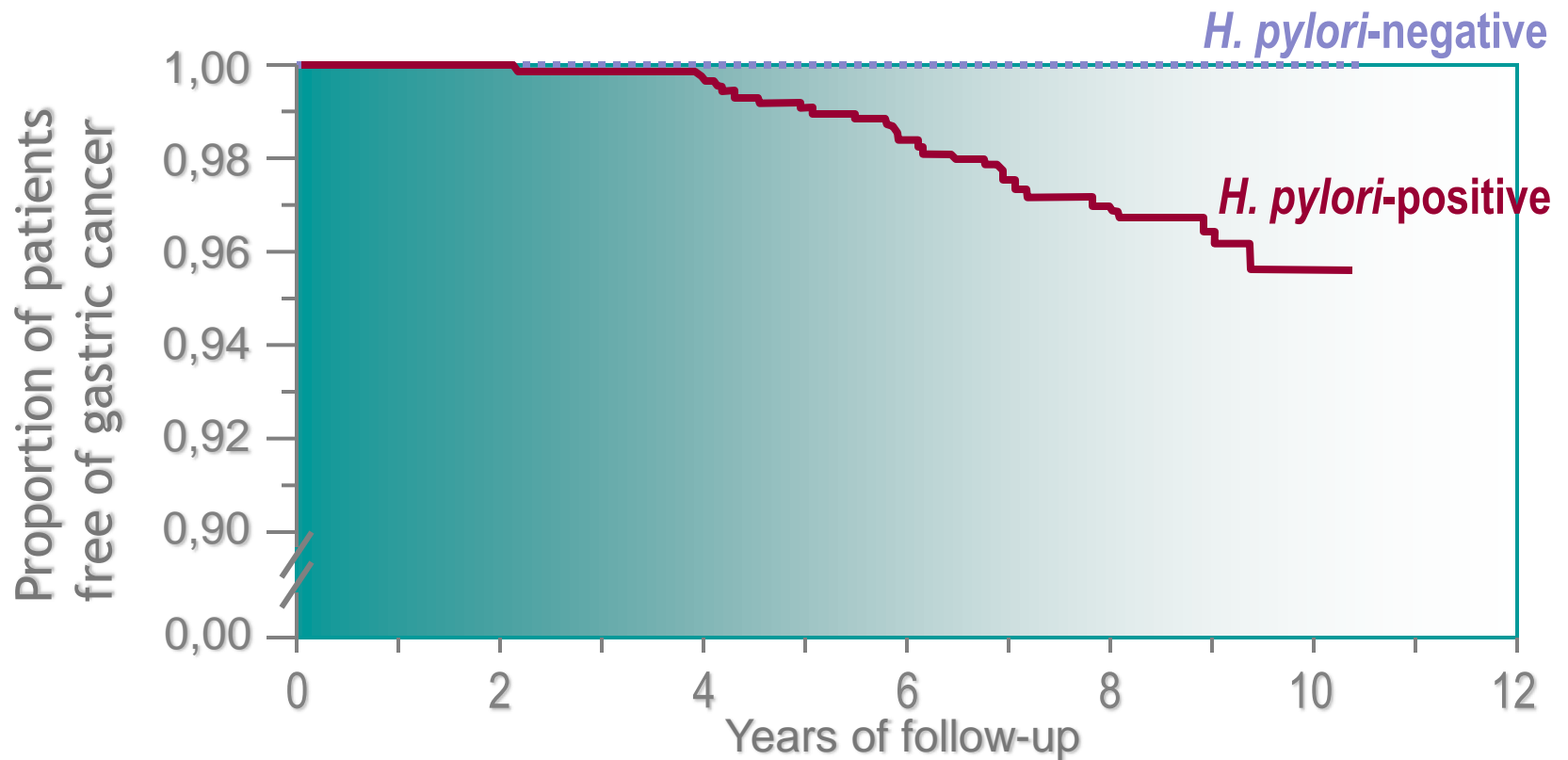


C Annual Incidence of Gastric Cancer (male)



Cases per 100,000 population

Development of gastric cancer according to *H. pylori* status



N at risk

<i>H. pylori</i> -negative	280	272	251	245	213	57
<i>H. pylori</i> -positive	1246	1219	1086	907	782	258

Uemura et al. N Engl J Med 2001;345:784-9

Development of gastric cancer in *H. pylori* positive patients according to histological abnormalities at base line

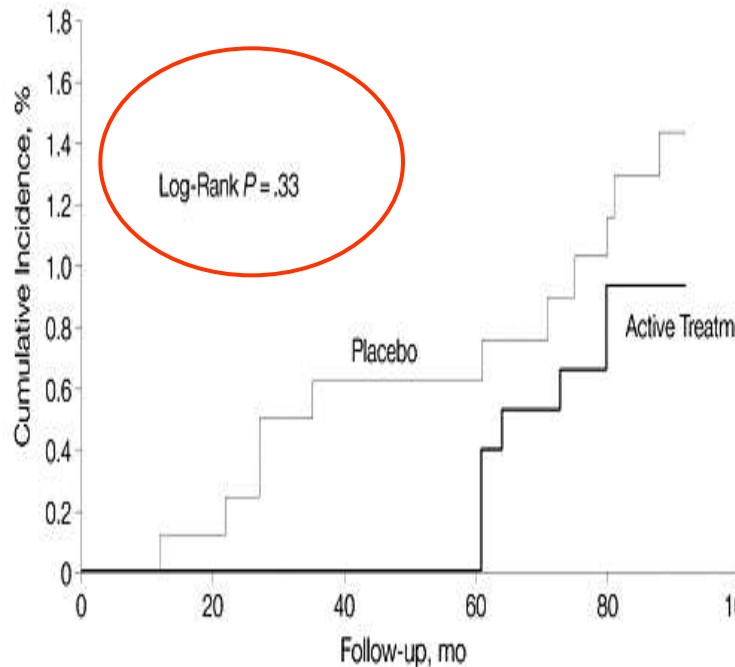
Abnormalities at base line	<i>H. pylori</i> positive (n=1246)	<i>H. pylori</i> positive with cancer (n=36)	Relative risk
	n°	(%)	
Grade of atrophy			
- none or mild	381	(0.8)	1.0
- moderate	657	(2.7)	1.7
- severe	208	(7.2)	4.9
Distribution of gastritis			
- antrum predominant	699	(0.3)	1.0
- pangastritis	337	(4.2)	15.6
- corpus predominant	210	(9.5)	34.5
Intestinal metaplasia			
- absent	782	(0.8)	1.0
- présent	464	(6.5)	6.4

Can *H pylori* eradication treatment reduce the risk for gastric cancer?

RCT comparing eradication vs placebo

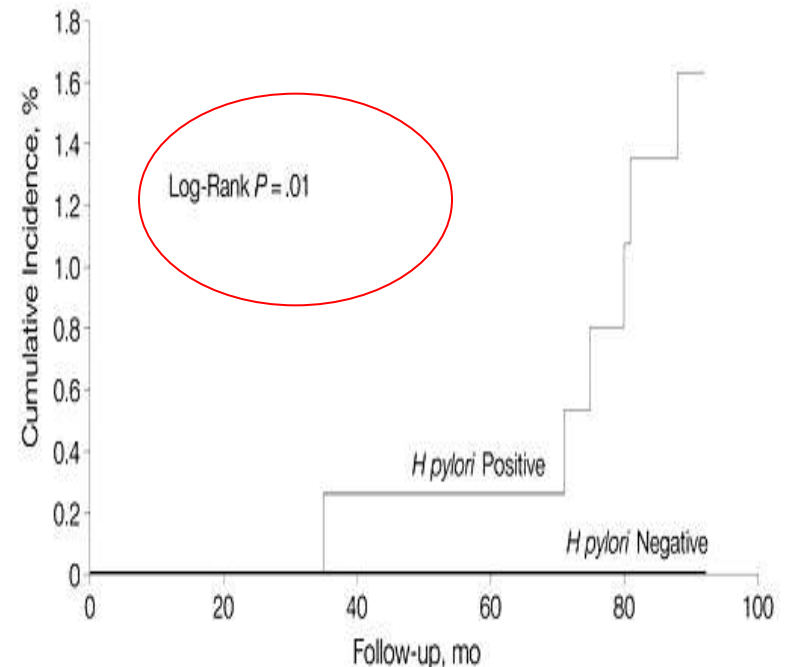
1,630 patients followed for 7.5 years in a high risk area (China)

All the patients



		No. at Risk				
		0	20	40	60	80
Active Treatment	817	806	798	790	747	
Placebo	813	790	781	774	741	

Patients without preneoplastic lesion



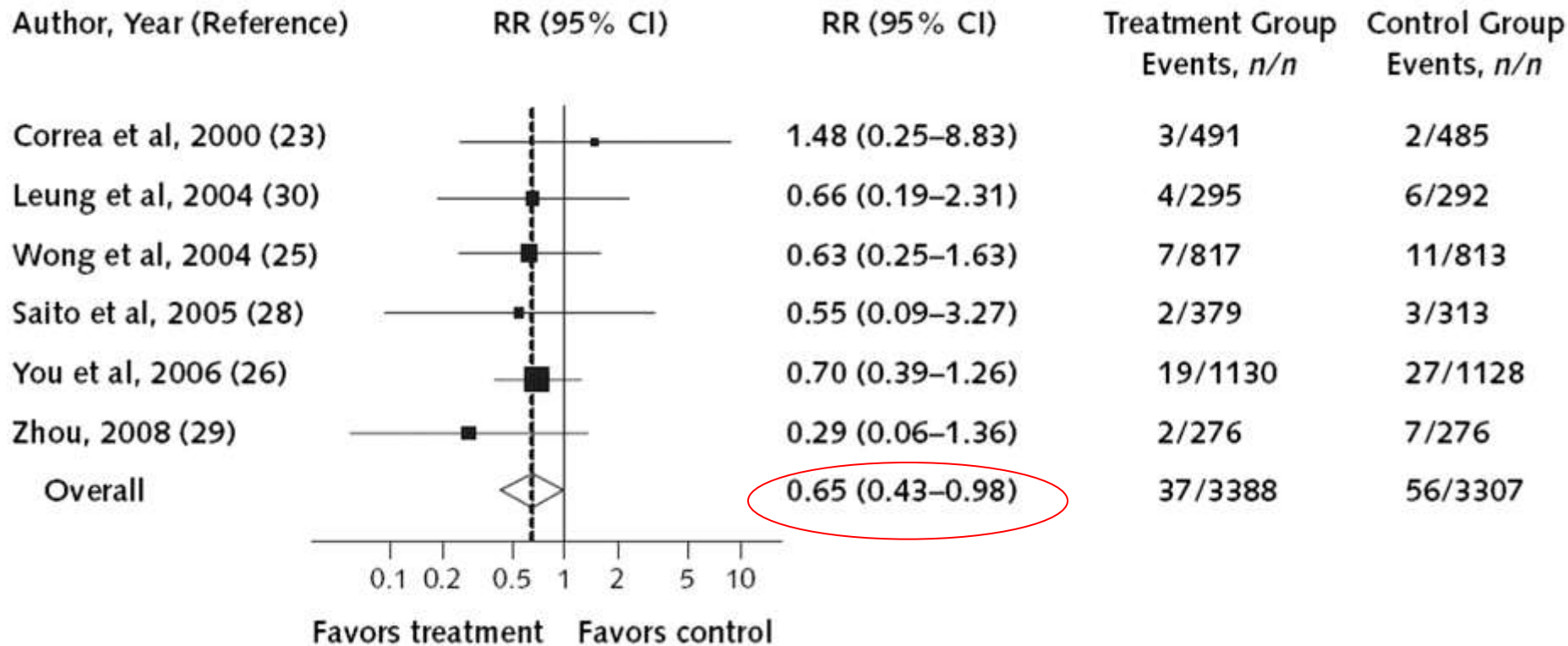
		No. at Risk				
		0	20	40	60	80
<i>H pylori</i> Positive	391	390	389	388	364	
<i>H pylori</i> Negative	413	412	409	406	383	

Effect of *H pylori* eradication on atrophy and intestinal metaplasia

Reference	country	n		Follow-up (months)	Atrophy in corpus	Intestinal metaplasia in corpus
Annibale et al 2002	Italy	40	NC	32-70	(8/40)improved	(8/40)improved
Ito et al 2002	Japan	26	NC	60	improved	improved
Kokkola et al 2002	Finland	22	NC	30	improved	improved
Leung et al 2002	China	587	RC	60	slowed progression	slowed progression
Correa et al 2000	Colombia	631	RC	72	RR for regression = 3.1 (IC95 % 1- 9,3)	

Can *H pylori* eradication reduce gastric cancer risk in patients with preneoplastic lesions

- Meta-analysis
- 6 RCTs (only 2 double-blinded)
- All studies in areas with high incidence of cancers (5 in Asia)
- Primary goal in five studies: to assess progression of preneoplastic lesions
- 6695 participants followed from 4 to 10 years



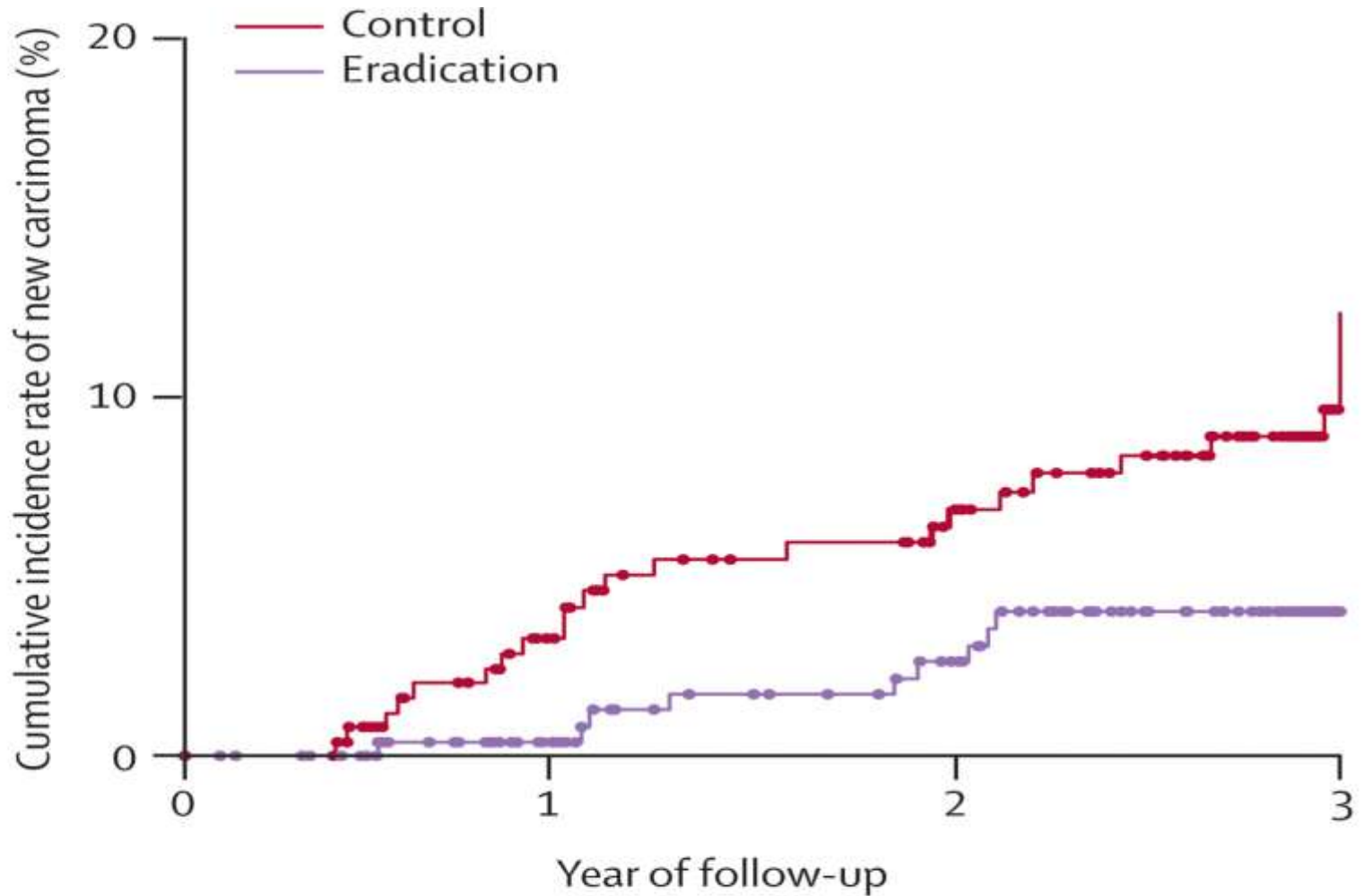
Forest plot of 6 studies reporting gastric cancer in treated and nontreated groups. The area of the boxes corresponds to the weight of each study.

Fuccio L et al. Ann Intern Med 2009;151:121-128

Effect of *H pylori* eradication on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer

- An open label, multicenter, randomized trial on the (n=544)
- 75% out of the patients with moderate or severe atrophy in the corpus
- 49% out of the patients with intestinal metaplasia in the corpus

The eradication therapy reduced the prevalence of secondary gastric cancer in a 3-year follow-up period HR 0.339, (95% CI 0.157- 0.729; p=0.003).



Number at risk

Control	250	250	213	167
Eradication	255	237	196	157

The long-term risk of gastric cancer persists after the successful eradication of *Helicobacter pylori*

- ***de Vries AC et al. Helicobacter pylori eradication and gastric cancer: when is the horse out of the barn? Am J Gastroenterol 2009;104(6):1342-5***

Two patients with gastric ulcer and intestinal metaplasia developed gastric cancer 4 years and 14 years after *H pylori* eradication

- ***Take S et al The long-term risk of gastric cancer after the successful eradication of Helicobacter pylori (Journal of Gastroenterology in press)***

1674 patients with peptic ulcer were followed for up to 14.1 years after *H pylori* eradication. Gastric cancer developed in 28 as long as 13.7 years after cure of *H pylori* infection. Severe gastric mucosal atrophy was clearly identified as a significant factor for the risk of developing gastric cancer

What should be the policy ?

- In countries with a high incidence rate of gastric cancer:
search and treat every infected subjects at a young age
- In countries with a low incidence rate of gastric cancer:
selection of persons at high risk

Patients at high risk in countries with a low incidence rate of gastric cancer

- Previous history of partial gastrectomy for cancer
- First degree relatives of patients with gastric cancer
- Patients on long-term treatment with PPI
- Patients with preneoplastic lesions (gastritis staging)

Gastritis staging: the OLGA system.

Two biopsies in the corpus, one at the incisura angularis, two in the antrum

		Corpus			
		No atrophy (score 0)	Mild atrophy (score 1)	Moderate atrophy (score 2)	Severe atrophy (score 3)
Antrum	No atrophy (score 0) (including incisura angularis)	Stage 0	Stage I	Stage II	Stage II
	Mild atrophy (score 1) (including incisura angularis)	Stage I	Stage I	Stage II	Stage III
	Moderate atrophy (score 2) (including incisura angularis)	Stage II	Stage II	Stage III	Stage IV
	Severe atrophy (score 3) (including incisura angularis)	Stage III	Stage III	Stage IV	Stage IV

Patients stage III and IV are at high risk of gastric neoplasia and needs *H pylori* eradication and endoscopic follow-up

Gastric cancer

Take home messages

- *H pylori* is the main cause of distal gastric cancer
- *H pylori* eradication can prevent gastric cancer
- Its efficiency is better in the absence of preneoplastic lesions
- In Europe, preventive *H pylori* eradication should be performed only in the patients at high risk
- Systematic biopsies in patients who undergo endoscopy is useful to select patients requiring *H pylori* eradication and endoscopic surveillance